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Role of Neurotrophins in the Development and Function of Neural Circuits that Regulate Energy Homeostasis

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Abstract

Members of the neurotrophin family, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), and other neurotrophic growth factors such as ciliary neurotrophic factor (CNTF) and artemin, regulate peripheral and central nervous system development and function. A subset of the neurotrophin-dependent pathways in the hypothalamus, brainstem, and spinal cord, and those that project via the sympathetic nervous system to peripheral metabolic tissues including brown and white adipose tissue (BAT and WAT), muscle and liver, regulate feeding, energy storage, and energy expenditure. We briefly review the role that neurotrophic growth factors play in energy balance, as regulators of neuronal survival and differentiation, neurogenesis, and circuit formation and function, and as inducers of critical gene products that control energy homeostasis.

Keywords

Brain-Derived Neurotrophic Factor (BDNF); Corticotropin Releasing Hormone (CRH); Hypothalamus; Nerve Growth Factor (NGF); Neurotrophin; VGF

Introduction

Neurotrophic growth factors contribute to the development of central and peripheral neural circuits that control energy balance, and also function in the adult nervous system to regulate circuit activity, neurogenesis, and gene expression. The sympathetic nervous system plays a critical role in the control of fat storage, glucose balance, and energy expenditure, through its innervation of many peripheral metabolic tissues; specific neurotrophins are required during discrete developmental windows to maintain neuronal viability and guide this circuit formation. We first review the developmental contributions of neurotrophins in the PNS, and then discuss how neurotrophic growth factors and the gene products they regulate control energy balance in the adult nervous system.

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Role of Neurotrophins in the Development of PNS Circuits that Control Energy Balance

Neurotrophin-3, Nerve Growth Factor, and Artemin

Postganglionic sympathetic neurons arise from neural crest cells that migrate and coalesce to form sympathetic ganglia and the sympathetic chain. Postganglionic sympathetic neurons innervate a variety of target tissues, including heart, adrenal, adipose, sweat and salivary glands, GI tract, liver and kidney, and these neurons are developmentally dependent on neurotrophins that regulate their survival, axonal outgrowth, and axonal targeting (Glebova and Ginty, 2005). Based on developmental analysis of neurotrophin-3 (NT-3) $-/-$ and artemin $-/-$ mice, NT-3 and the glial-derived neurotrophic factor (GDNF) family member artemin regulate proximal axonal extension of sympathetic neurons along blood vessels, from the sympathetic ganglia to the target tissue (Honma et al., 2002; Kuruvilla et al., 2004). While NT-3/TrkA signaling is required for proximal axonal extension along arterial vasculature, NGF/TrkA signaling is crucial for distal axonal extension, axonal branching and target innervation, and neuronal survival (Glebova and Ginty, 2004). Target-derived BDNF on the other hand has been suggested to function as an inhibitor of sympathetic outgrowth and/or inappropriate target innervation, through its interaction with the p75 neurotrophin receptor (p75NTR) in the absence of both TrkB receptor expression and robust NGF/TrkA activation (Huang and Reichardt, 2001). Moreover, sympathetic axons that successfully find targets secrete BDNF in an activity-dependent fashion, which then binds to p75NTR on less active competing axons, leading to degeneration and axon pruning (Singh et al., 2008). Recent studies suggest that distinct NGF/TrkA and NT-3/TrkA signaling endosomes, which differentially recruit Rac1-GTP-cofilin actin modifiers, govern retrograde NGF signaling and survival of sympathetic neurons (Harrington et al., 2011). Retrograde survival signals such as NGF, other neurotrophins including BDNF and NT-4, and neuronal activity, have roles in the formation of dendrites from the postganglionic neuron and the establishment of synapses between pre- and postganglionic neurons within the sympathetic ganglion (Glebova and Ginty, 2004). Perhaps least understood at the neuroanatomical, developmental, and functional levels is the formation of connections between postganglionic sympathetic neurons and target tissues, other than the recognition that these varicosities are not classical synapses, and that target-derived neurotrophins such as NGF are required to complete the process of innervation.

Role of Neurotrophins in the Regulation of CNS Circuits that Control Energy Balance

Brain-Derived Neurotrophic Factor

Hypothalamic—brainstem (rostroventrolateral medulla/raphe pallidus)—intermediolateral horn spinal cord—sympathetic preganglionic—sympathetic postganglionic pathways to adipose depots, liver, and muscle regulate energy storage and expenditure. In adipose tissue, sympathetic neurons terminate on blood vessels and on adipocytes; sympathetic nerve activity regulates energy expenditure in BAT and lipolysis in WAT primarily through release of norepinephrine that binds to specific beta-adrenergic receptors on the adipocyte cell surface, a process that is modulated by secreted neuropeptides (Turtzo et al., 2001; Collins et al., 2004). In addition to their roles in development, neurotrophins make critical functional contributions in the adult CNS, particularly in these hypothalamic outflow pathways. Brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB) are widely expressed in the CNS, notably in the hypothalamic ventromedial nucleus, lateral hypothalamic area, dorsomedial nucleus (DMN) and paraventricular nucleus (PVN), where BDNF signaling regulates energy balance (Tapia-Arancibia et al., 2004;

Levin, 2007; Noble et al., 2011). Analysis of obese, hyperphagic heterozygous knockout and conditional knockout mice with reduced expression of BDNF or the BDNF receptor TrkB, indicated that BDNF functions in a catabolic manner, increasing energy expenditure and reducing food intake (Kernie et al., 2000; Rios et al., 2001; Xu et al., 2003; Unger et al., 2007). Consistent with knockout mouse studies, acute administration of BDNF into the adult rat hypothalamic paraventricular nucleus (PVN) increased energy expenditure (Wang et al., 2007c) and reduced energy intake while also blocking NPY-induced feeding (Wang et al., 2007b). Injection of BDNF into the ventromedial hypothalamic nucleus (VMN) (Wang et al., 2007a) and dorsal vagal complex of the brainstem (Bariohay et al., 2005) similarly reduced food intake. These studies regionally localized the effects of BDNF on energy balance, refining previous findings of reduced food intake and body weight following chronic systemic and intracerebroventricular administration of BDNF to rats (Lapchak and Hefti, 1992; Pelleymounter et al., 1995), and normalization of glucose metabolism and energy balance in obese, diabetic *db/db* mice administered subcutaneous and in some cases intracerebroventricular BDNF (Nakagawa et al., 2000; Tsuchida et al., 2001; Tsuchida et al., 2002). Extending these results to humans, female patients with type 2 diabetes mellitus were found to have increased serum BDNF levels (Suwa et al., 2006), which positively correlated with body mass index, percentage of body fat, and fasting blood glucose levels.

Hypothalamic BDNF expression is also required to transduce effects of environmental enrichment on WAT, leading via increased sympathetic nervous system activity to increased numbers of brown adipocytes in WAT (i.e. white fat “browning”), increased energy expenditure, and a lean, obesity-resistant phenotype in mice (Cao et al., 2011). Moreover, endogenous synthesis of BDNF from dendritically targeted BDNF mRNA in the VMH plays a critical role in energy balance and the response to leptin (Liao et al., 2012). Mice in which this BDNF mRNA with a long 3' untranslated region (3' UTR) is selectively ablated, while short 3'UTR BDNF transcripts that are restricted to the neuronal cell body are retained, were found to be obese, hyperleptinemic, with enlarged adipose tissue depots and impaired glucose homeostasis (Liao et al., 2012). The observation that severe hyperphagic obesity in these mice was completely reversed by viral expression of long 3' UTR BDNF mRNA in the VMH argues for a functional rather than developmental role for dendritically targeted BDNF transcripts to regulate adult hypothalamic circuits in the VMH, DMH, and arcuate nucleus that control energy balance.

Ciliary Neurotrophic Factor

Members of the ciliary neurotrophic factor (CNTF)-leukemia inhibitory factor (LIF) family play an essential, cooperative role in motoneuron survival and function (Holtmann et al., 2005), and recombinant CNTF was first discovered to modulate energy balance in a therapeutic trial for the treatment of the motoneuron disease amyotrophic lateral sclerosis (ALS) (ACTS, 1996; Miller et al., 1996). Subsequent studies using a modified form of recombinant CNTF with improved potency and stability (Axokine) confirmed that administration resulted in decreased food intake and weight loss, and further demonstrated improvement in the hyperglycemia, hyperinsulinemia, and hyperlipidemia that are associated with obesity [reviewed in (Matthews and Febbraio, 2008; Allen et al., 2011)]. Persistent weight loss even after CNTF administration was discontinued (Seeley, 2005) led to an investigation of CNTF function in the brain and the recognition that this neurotrophin regulated neurogenesis within critical hypothalamic feeding centers (Kokoeva et al., 2005). The newly integrated neurons produced by CNTF treatment expressed the neuropeptides POMC or AgRP/NPY, and also showed enhanced signaling responses to leptin, which resulted in the sustained weight loss. Thus the mechanism(s) by which CNTF regulates energy balance involve central effects on hypothalamic neurogenesis and peripheral effects on multiple tissues, including muscle, liver, and adipose, to improve insulin sensitivity,

increase thermogenesis, increase energy expenditure, and increase fat oxidation (Matthews and Febbraio, 2008; Allen et al., 2011).

Neurotrophin Regulation of Downstream Gene Products that Modulate Energy Balance

Granins and Neuropeptides

Neurotrophins control energy balance by modulating the hypothalamic/sympathetic circuits that connect the CNS to peripheral metabolic tissues, in large part through the gene products they regulate. NGF and BDNF are produced in adipose tissue, for example, and have also been proposed to function not only as neurotrophins, but as metabotrophins, proteins which are secreted in an endocrine fashion that control lipid metabolism, and glucose and energy balance (Chaldakov et al., 2009). VGF (nonacronymic) is an NGF-, NT-3, and BDNF-inducible secreted neuronal and endocrine protein and peptide precursor (Levi et al., 1985; Levi et al., 2004), a member of the extended chromogranin/secretogranin family (Bartolomucci et al., 2011), that plays a significant role in the control of energy homeostasis (Hahm et al., 1999). Homozygous mice with targeted germline deletion of *Vgf* were noted to be lean and hypermetabolic, had body weights ~60% of their wild type littermates, and resisted diet-, lesion-, and genetically-induced obesity, hyperglycemia, and hyperinsulinemia (Hahm et al., 1999; Hahm et al., 2002; Watson et al., 2005). WAT stores were also reduced, suggesting increased lipolysis, and uncoupling protein 1 (UCP-1) protein levels and mitochondrial number were increased in BAT, consistent with increased thermogenesis and energy expenditure (Watson et al., 2009). Peripheral neonatal sympathectomy blocked the development of the lean VGF knockout phenotype, indicating a role for VGF in the regulation of hypothalamic/sympathetic outflow pathways (Watson et al., 2009). Interestingly, neuropeptides cleaved from the VGF precursor, including the amidated NERP peptides and several C-terminal neuropeptides (TLQP62, TLQP21 and AQEE30), differentially regulate feeding and energy expenditure, with either anabolic or catabolic bioactivities (Toshinai et al., 2010; Possenti et al., 2012). NERP-2 increased feeding and energy expenditure via an orexin-dependent pathway (Toshinai et al., 2010), TLQP21 modulated beta-adrenergic signaling in WAT leading to increased lipolysis (Possenti et al., 2012), and TLQP62 may regulate BDNF release and/or processing, at least in hippocampus, where this peptide stimulated electrical potentiation (Bozdagi et al., 2008) and neurogenesis (Thakker-Varia et al., 2007). Additional studies utilizing conditional VGF knockdown or knockout approaches are required to tease apart the functional roles for this protein during development and in the adult, much has been accomplished for BDNF.

Corticotropin Releasing Hormone CRH and Glucocorticoids

The mechanisms by which neurotrophins control energy homeostasis are incompletely understood, but most likely involve the modulation of neuropeptides and neurotransmitters that are established molecular regulators of feeding and energy expenditure. BDNF is a known downstream effector of melanocortin signaling in the brain, in both hypothalamus and brainstem (Xu et al., 2003; Bariohay et al., 2009). BDNF stimulates neuropeptide synthesis and release from hypothalamic neurons, including somatostatin, arginine vasopressin (AVP), and corticotropin releasing hormone (CRH) (Tapia-Arancibia et al., 2004; Levin, 2007; Noble et al., 2011), reducing food intake and body weight via a CRH pathway when infused into the PVN (Toriya et al., 2010). Recent studies have demonstrated that expression of CRH, the principle regulator of the hypothalamic-pituitary-adrenal (HPA) axis, is regulated in the PVN positively by BDNF-TrkB-cAMP response-element binding protein (CREB) signaling and negatively by glucocorticoid-glucocorticoid receptor-cAMP response-element binding protein coactivator CRTC2 signaling (Jeanneteau et al., 2012). Crosstalk allows integration of the HPA axis and glucocorticoid control of energy intake,

storage, and mobilization (Dallman et al., 2004), with neurotrophin signaling pathways, to more effectively modulate the central and peripheral neuronal circuits that regulate feeding and energy expenditure.

Conclusions

In this mini-review we have highlighted the critical developmental and functional roles that neurotrophic growth factors play to control energy uptake and expenditure. In addition to supporting cell viability and directing circuit formation early in development, growth factors like BDNF and CNTF contribute directly to the maintenance of energy balance and glucose homeostasis in the adult, where they regulate signaling pathways, leading to altered expression of downstream gene products and even increased neurogenesis. These downstream effectors, including neuropeptides such as CRH and granin proteins like VGF, modulate hypothalamic outflow pathway activity to regulate energy balance. Their precise mechanisms of action are currently under intense investigation, as they may offer novel treatment modalities for obesity and diabetes.

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Figure 1.

Neurotrophin Regulation of Energy Balance in the Adult CNS and PNS. This diagram summarizes the effects of peripherally administered CNTF (Axokine), and centrally as well as peripherally administered BDNF (black arrows), on adult CNS and sympathetic circuits that control energy intake and expenditure. Administration of BDNF or BDNF-transducing viruses to the PVN and other hypothalamic regions increases sympathetic outflow pathway activity, resulting in increased energy expenditure and decreased feeding, as discussed in this mini-review. CRH pathways (white arrow) integrate these BDNF signals with those from the HPA axis to modulate energy balance. Circulating CNTF has been shown to directly effect peripheral metabolic activity, and in the CNS, to regulate the neurogenesis of critical leptin-responsive, POMC- and NPY/AgRP-containing neurons in hypothalamic circuits that regulate feeding and energy homeostasis.